A higher altitude is an independent risk factor for venous thromboembolisms following total shoulder arthroplasty

Dhanur Damodar^{a,*}, Rushabh Vakharia^b, Ajit Vakharia^c, Jon Sheu^a, Chester J. Donnally III^a, Jonathan C. Levy^b, Lee Kaplan^a, Julianne Munoz^a

^a University of Miami Hospital, Department of Orthopedic Surgery, 1400 N.W. 12th Ave, Miami, FL, 33136, USA

^b Holy Cross Hospital, Orthopedic Research Institute, 5597 North Dixie Highway, Ft. Lauderdale, FL, 33308, USA

^c Morehouse School of Medicine, 720 Westview Dr., 30310, Atlanta, GA, USA

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ABSTRACT

Introduction: High altitudes lead to physiological changes that may predispose to venous thromboembolisms (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE). No prior study has evaluated if there is also a higher risk of VTEs after total shoulder arthroplasties (TSAs) performed at higher elevations compared to lower elevations. The purpose of this study was to identify if undergoing TSA at a higher altitude center (> 4000 feet above sea level) is an independent risk factor for a postoperative VTE.

Methods: A retrospective review was performed from 2005 to 2014 using the Medicare Standard Analytical Files of the Pearl Diver database (Pearl Diver Technologies, West Conshohocken, PA, USA). The inclusion criteria for the study group consisted of all patients in the database undergoing primary TSAs at an altitude above 4000 feet. Patients were queried using the International Classification of Disease 9th revision codes (ICD-9). All patients undergoing primary TSA were queried using ICD-9 procedure code 81.80. Patients were filtered using the zip codes of the hospitals where the procedure occurred and were separated into high (> 4,000 ft) and low (< 100 ft) altitudes. Patients undergoing TSA in altitudes < 100 ft represented the control group. Patients with a history of VTE, DVT, PE, and coagulation disorders were excluded from the study. Patients in the study group were randomly matched 1:1 according to age, gender, and comorbidities. Two mutually exclusive cohorts were formed and rates of VTE, DVT, and PE were analyzed and compared. Statistical analysis was performed using the programming language R (University of Auckland, New Zealand). An alpha value less than 0.05 was considered statistically significant.

Results: In the first 30 postoperative days, patients undergoing TSA at a higher altitude experienced a significantly **higher** rate of PEs (odds ratio [OR], 39.5; $P = < 0.001$) when compared to similar patients at lower altitudes. This trend was also present for PE (OR, 2.02; $P < 0.03$) at 90 days postoperatively.

Conclusion: TSAs performed at higher altitudes (> 4000 feet) have a **higher** rate of acute postoperative PEs in the first 30 days and 90 days postoperatively when compared to matched patients receiving the same surgery at a lower altitude (< 100 feet). TSA patients at high altitude should be counseled on these increased risks.

1. Introduction

Venous thromboembolism (VTE) is a well recognized complication of Total Hip and Total Knee Arthroplasties (THA and TKA),¹ however considered to be a rare complication after Total Shoulder Arthroplasty (TSA). Deep Venous Thrombosis (DVT) rates can be as high as 40–60% and Pulmonary Embolism (PE) rates can be as high as 1–3% after THA and TKAs.² However, VTE rates after TSA have been shown to be between 0.2% and 16.0%.³ In contrast to THAs and TKAs which have established guidelines published by the AAOS and ACCP,^{4,5} TSAs lack

formally published guidelines or protocols for post-operative VTE prophylaxis. Thus, the routine use of chemical prophylaxis following TSA is rare.

Most orthopedic surgeons properly optimize high risk patients at increased risk for VTEs, which includes those with: obesity (BMI 30), tobacco use, hypertension, diabetes mellitus, and hyperlipidemia.⁶ One risk factor for post-operative VTEs that has been demonstrated in other orthopedic procedures is altitude, with the assumption that higher altitudes may increase risk for VTE. While this has been evaluated for post-operative orthopedic patients undergoing acute air travel, the

* Corresponding author. University of Miami, Department of Orthopedics, 1400 NW 12th Ave, Miami, FL, 33136, USA.

E-mail address: ghanur.damodar@jhsMiami.org (D. Damodar).

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impact of high altitude has not been investigated in TSA patients.⁷

Higher altitudes lead to physiologic changes that may predispose to VTE including DVT and pulmonary embolism (PE). Several studies have demonstrated an increase in factors contributing to Virchow's Triad (hypercoagulability, venous stasis, and vessel wall injury) at high altitudes.^{8–10} Prior studies have noted increased rates of VTE in patients undergoing arthroscopic knee and shoulder surgery at high altitude centers (> 4000 feet) compared to low altitude centers (< 100 feet).^{11–13} To date, no paper has evaluated if there is also a higher risk of VTEs for TSA procedures performed at higher elevations compared to lower elevations.

The purpose of this study is to evaluate whether high altitude is a potentially modifiable risk factor following TSA by comparing the rates of deep vein thrombosis (DVT), pulmonary embolisms (PE) and VTEs in patients undergoing TSA at a high and low altitude centers. Our hypothesis is that patients undergoing TSA at higher altitudes will have higher incidence of VTEs than patients at lower altitudes.

2. Materials and methods

A retrospective study was done utilizing the national provider database Pearl Diver (Pearl Diver Technologies, Inc. Fort Wayne, Indiana), which is compliant with the Health Insurance Portability and Accountability Act. Pearl Diver is a publicly available database that holds the records of over 23 million patients. The International Classification of Disease, ninth edition (ICD-9) codes for total shoulder arthroplasty (TSA, 81.80) and reverse shoulder arthroplasty (RSA, 81.88) facilitated a selective query of the entire Medicare population was performed from 2005 to 2014.

Patients were stratified into two groups based on the altitude of the hospital. Those who had the procedure in areas with high altitude > 4000 feet were defined as the “high altitude group” and the control group which had the procedure at < 100 feet, were defined as the “low altitude group”. 5-digit zip codes provided through the Zip-Codes database (Datasheet LLC, Hopewell Junction, NY, USA) provided the geographic locations of the U.S. mainland with respect to altitude (Fig. 1). An assumption was made that zip code of procedure was the

same as zip code of recuperation for these patients. Our exclusion criteria included those patients with a prior history of deep venous thrombosis (DVT) and/or pulmonary embolism (PE), as well as patients with a prior history of a hypercoagulable state or with any unspecified coagulation defect (ICD-9 codes 298.81, 289.82, and 286.9).

Using Boolean operations, patients in the high altitude group were matched controlled with patients in the low altitude group. Patients were matched based on comorbidities which are known to lead to thromboembolic events, including BMI > 30, tobacco use, hypertension, diabetes, and hyperlipidemia.⁶

The matching process is done 1:1 based on age, sex, and the five comorbidities known to be associated with increased risk of post-operative VTE as noted above. Rates of DVT and PE were assessed in both groups within 30-days and 90-days of the above stated procedures. Descriptive and statistical analysis was performed by the programming language R (University of Auckland, New Zealand).

Statistical analysis included calculating odds ratios (OR) and 95% Confidence Intervals (CI) using binary logistic regression. Analyses where one group contained an event rate of zero were performed using Fisher's Exact Test, and the odds ratio manually calculated using a 2 × 2 table. Risk ratios (RR) were calculated from odds ratios and event prevalence in the low-altitude group. Number needed to harm (NNH) was calculated from event incidence in both groups. Statistical significance was defined as $p < 0.05$.

3. Results

A total of 37,819 TSA patients met all inclusion criteria before breakdown by zip code. 7754 patients had their procedures performed at an altitude of greater than or equal to 4000 feet and formed the high-altitude study group. 30,065 patients had their procedures performed at an altitude of less than or equal to 100 feet and formed the low-altitude study group. Of these, 13,964 age- and gender-matched patients (Table 1) were identified for inclusion in this study.

For patients undergoing TSA, the overall VTE rate within 30 days was 0.27%; the overall DVT rate within 30 days was 0.0% and the overall PE rate within the same time frame was 0.27% (Table 2). Within

Fig. 1. Geographic United States with varying altitudes used in the study.

Table 1
Patient demographics by age, gender, and comorbidities.

Demographic Characteristics	n (%)
Total	7602
Sex	
Male	3320 (43.7)
Female	4197 (55.2)
Unknown	85 (1.1)
Age	
< 64	572 (7.5)
65–69	2100 (27.6)
70–74	1967 (25.9)
75–79	1590 (20.9)
80–84	960
> 85	328 (4.3)
Unknown	85 (1.1)
Comorbidities	
Hyperlipidemia	4932 (64.9)
Diabetes Mellitus	2815 (37.0)
Hypertension	6435 (84.6)
Tobacco User	890 (11.7)
Body Mass Index ≥ 30	2080 (27.4)

Table 2

Comparison of Thromboembolic Complications 30- and 90-days following Primary Total Shoulder Arthroplasty in High Altitudes (> 4,000 ft) and Low Altitudes (< 100 ft). OR: Odds-Ratio; 95%CI: 95% confidence interval; VTE = Venous Thromboembolism; DVT = Deep Vein Thrombosis; PE = Pulmonary Embolism.

30 days post-operatively	> 4000 ft n (%)	< 100 ft n (%)	OR	95%CI	p-value
Total patients	6948	7016	–	–	–
VTE	19 (0.27)	0 (0.00)	39.48	2.38–654.19	< 0.0001
DVT	0 (0.00)	0 (0.00)	–	–	–
PE	19 (0.27)	0 (0.00)	39.48	2.38–654	< 0.001
90 days post-operatively	> 4000 ft n (%)	< 100 ft n (%)	OR	95%CI	p-value
Total patients	6948	7016			
VTE	43 (0.62)	26 (0.37)	1.67	1.02–2.72	0.038
DVT	15 (0.22)	12 (0.17)	1.26	0.59–2.69	0.547
PE	28 (0.40)	14 (0.20)	2.02	1.06–3.84	0.0315

90 days, the overall VTE rate rose to 0.62%; the overall DVT rate within 90 days rose to 0.22%, and the overall PE rate within the same time frame rose to 0.40%.

Within the first 30 days, the overall VTE and PE rates in patients undergoing TSA at higher altitudes was significantly higher (OR 39.49; $P < 0.0001$) when compared to similar patients at lower altitudes (Fig. 2, Table 2). This was also true for the overall VTE (OR 1.67; $P = 0.0385$) and PE rates (OR 2.02; $P = 0.0315$) at 90 days post-operatively (Fig. 3, Table 2). The risk of VTE was elevated at both 30 (risk ratio [RR] 39.49) and 90 days (RR 1.67) postoperatively. The DVT incidence was 0.0% at 30 days in both low and high altitude groups. The DVT incidence was 0.17% and 0.12% in the low and high altitude groups, respectively, at 90 days postoperatively without significance. The Number Needed to Harm (NNH) for a VTE at 30 days was 364.7; at 90 days it was 398.8. The risk of PEs was elevated at both 30 (RR 39.49) and 90 days (RR 2.02) postoperatively. The NNH for a PE at 30 days was 364.7; the at 90 days was 488.6. There were no observed DVTs within 30 days; despite an increased incidence by 90 days, the difference between high and low altitude was not significant ($P = 0.5473$).

4. Discussion

In this study, we found Medicare patients undergoing TSA were 39.5 and 2.02 times more likely to have postoperative PEs at higher

Fig. 2. Comparison of venous thromboembolism in patients undergoing primary total shoulder arthroplasty in high altitude or low altitude.

Fig. 3. Comparison of venous thromboembolism, deep vein thrombosis, and pulmonary embolism in patients undergoing primary total shoulder arthroplasty in high or low Altitudes.

VTE = venous thromboembolism; DVT = deep vein thrombosis; PE = pulmonary embolism.

elevations compared to matched controlled patients treated in centers at sea level (< 1000 feet) within 30- and 90-days of their procedures, respectively. There were no differences in DVT rates at 30 and 90 days after surgery.

The physiological effect of higher altitude on the human body is thought to be one of the factors that may predispose patients to higher VTE rates.^{8–10,14–16} As one would expect, the body undergoes a host of physiologic changes as it enters a high altitude environment. First it compensates by changing its ventilation rate. As the body adjusts, changes then occur to the oxygen-hemoglobin dissociation curve in order to adapt to the lower oxygen levels. Results from high altitude studies show that environmental conditions such as hypoxia, dehydration, hemoconcentration, decreased temperature, use of constrictive clothing as well as venous stasis due to severe weather all support the possible occurrence of thrombotic disorders.⁷

Anand et al. reported a 30 times increased risk of spontaneous vascular thrombosis amongst soldiers stationed at high altitude for an extended period of time.¹⁶ Some studies have suggested changes at high altitude can cause activation of the coagulation cascade and lead to increased thrombosis. A recent study looked at patients at a high altitude (over 3500 feet) and concluded that several factors, including: erythrocytosis, elevated platelet level and increased platelet activation, as well as raised fibrinogen levels in conjunction with hypoxia and dehydration create a thrombotic milieu which cause increased rates of VTE.¹⁷

In the orthopedic literature, Tyson et al. reviewed 35,877 patients undergoing knee arthroscopy at 1000 feet vs 4000 feet and determined those at 4000 feet (high elevation cohort) were at a significantly higher risk of DVT, but not PE.¹⁰ Similarly, Cancienne reviewed 64,291 patients undergoing knee arthroscopy; their low altitude cohort underwent procedures performed at or below 100 feet. They found that at both 30 and 90 days postoperatively the rates of VTE, DVT and PEs were increased in the higher altitude cohort.¹¹ Most recently, Cancienne also reviewed 6322 Arthroscopic rotator cuff repairs at high altitude matched with low altitude rotator cuff repairs, and found that rates of VTEs, PEs and lower extremity DVTs were all significantly higher in the high altitude group at 90 days postoperatively. This is the only study in the literature looking at upper extremity surgery at high altitude and the effect on rates of VTE.

The current standard of care is no chemoprophylaxis after TSA. In the largest cohort of TSAs studied for VTEs, Day et al.¹⁸ reviewed 100,000 Medicare patients that underwent TJA and TSA. They found that VTE rates after TSA (0.53%) are lower than VTE rates after lower extremity arthroplasty (1.2%). Prior history of VTE, presence of a metastatic tumor, and cardiac arrhythmia were identified as consistent risk factors for VTEs after TJA and TSA. The risk of a wound hematoma as a complication of chemoprophylaxis of TSA did not differ significantly between the two groups. Based on these results, the authors concluded routine anticoagulation is not necessary after TSA. An important consideration is that the lower incidence of thromboembolic events in TSA may cause decreased surveillance of these patients post-operatively.

A recent systematic review looked at VTE after TSA and found 6/14 (43%) eligible articles used some form of thromboprophylaxis. Mechanical prophylaxis was used in all 6 studies, chemical prophylaxis however was only used in 2/14 studies (14%).¹⁹ In one of the two studies, Willis et al.²⁰ used Aspirin 325 mg twice daily for prophylaxis. In the other study, Jameson et al.²¹ used low-molecular-weight heparin (LMWH). Prophylaxis was used in those two studies based on risk factors determined by the authors, including but not limited to: elevated BMI, advanced age, history of VTE, elevated Charlson Comorbidity Index (CCI), and time spent in the operating room. The authors advocated for use of mechanical prophylaxis in all patients after TSA, however no recommendations could be made for use of chemoprophylaxis based on the data.

The study mentioned above by Willis et al.²⁰ was a prospective observational study that reviewed postoperative DVT and PE rates after TSA in 100 patients. They found a 12% rate of DVT and a 3% rate of PEs. Postoperative prophylaxis consisted of Aspirin 325 twice a day, pneumatic compression foot pumps, and early ambulation. No pre-operative risk factors in this study approached significance due to the limited sample size, however the rate of thromboembolic events demonstrates the need for increased vigilance in patients undergoing TSA.

The beach chair positioning during TSA and its role in venous stasis was studied by Saleem et al.²² They suggested that positioning during a TSA can cause kinking of the femoral veins due to flexion of the thighs and lead to dependent pooling of blood within the lower extremities. This may lead to increased venous stasis and increased rates of lower extremity DVT post-operatively. Surgeons must take note of this risk, especially if a case is prolonged, and the intraoperative time in the beach chair position increases.

A recent study by Tasjian et al.²³ found that lower preoperative Hemoglobin and Hematocrit levels can be a significant risk factor for postoperative VTE. This finding is in contrast to the physiologic studies of high altitude which note that changes circulation, causing erythrocytosis, can lead to increased risk of VTE. Here, the authors found that lower preoperative hemoglobin can be an associated risk factor for postoperative VTE.

There is a need for a TSA specific risk stratification system to be developed to optimize these patients preoperatively. While TJA has several risk stratification systems and published guidelines for VTE prophylaxis, patients undergoing TSA and other ambulatory surgical

procedures are often not given an appropriate preoperative VTE risk assessment due to the lack of established guidelines. We are not suggesting that chemoprophylaxis be instituted at high altitudes, however this study gives us a modifiable risk factor in TSA patients that should be taken into consideration preoperatively.

This study has several limitations. As with all database studies, this review is potentially flawed by human error as it requires the input of various data points into a complex coding system, creating many opportunities for faulty coding or under reporting. While this may under report actual VTE rates, theoretically these errors would occur at equal rates in both cohorts.

Furthermore, the database does not specify how VTEs were diagnosed (Doppler ultrasound, clinically, or otherwise), whether surgeons at higher altitude are more likely to use one diagnostic technique over another, or whether surgeons at different altitudes were more or less rigorous with their postoperative VTE prophylaxis. Use of VTE prophylaxis in the postoperative period is controversial and often no chemoprophylaxis is typically used by shoulder surgeons, therefore we were unable to compare any discrepancies in our cohorts that may bias one group. Although this is a matched controlled study with a multivariate analysis, and while we controlled for several risk factors, there are also several risk factors we could not account for including use of hormonal replacement therapy, type of prophylaxis used, family history of VTE, and length of surgery which could all influence the final results. Finally, the odds ratio of 39.5 is likely a result of the $n = 0$ in the low altitude group at 30 days post-operatively. This finding must be interpreted with caution, as the zero events likely led to an inflated odds ratio.

5. Conclusion

Our study of Medicare patients demonstrates a significantly increased risk of PEs in postoperative TSA patients at altitudes greater than 4000 feet. Although the incidence of VTE events in TSA patients is much lower than other lower extremity orthopedic procedures, high altitude should be thought of as an additional factor included in pre-operative risk stratification of patients undergoing elective TSA. It is important to note however, that there was no significant difference in DVTs. Our results suggest high altitude may predispose patients to PE events after TSA, however due to confounding variables that cannot be assessed retrospectively, further prospective studies are warranted to evaluate this outcome in more detail.

Conflict of interest

The authors declare there are no conflicts of interest.

Conflicts of interest and source of funding

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All authors significantly contributed to the document and have reviewed the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jor.2018.09.003>.

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